



Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection (Last Updated April 14, 2020; last reviewed April 14, 2020)

Panel's Recommendations

- All newborns who were perinatally exposed to HIV should receive postpartum antiretroviral (ARV) drugs to reduce the risk of perinatal transmission of HIV (AI).
- Newborn ARV regimens administered at doses that are appropriate for the infant's gestational age should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery (AII).
- A newborn's ARV regimen should be determined based on maternal and infant factors that influence the risk of perinatal transmission of HIV (AII). The uses of ARV regimens in newborns include:
 - ARV Prophylaxis:** The administration of one or more ARV drugs to a newborn without documented HIV infection to reduce the risk of perinatal acquisition of HIV.
 - Presumptive HIV Therapy:** The administration of a three-drug ARV regimen to newborns who are at highest risk of perinatal acquisition of HIV. Presumptive HIV therapy is intended to be preliminary treatment for a newborn who is later documented to have HIV, but it also serves as prophylaxis against HIV acquisition for those newborns who are exposed to HIV *in utero*, during the birthing process, or during breastfeeding and who do not acquire HIV.
 - HIV Therapy:** The administration of a three-drug ARV regimen at treatment doses (called antiretroviral therapy [ART]) to newborns with documented HIV infection (see [Diagnosis of HIV Infection in Infants and Children](#)).
- A 4-week zidovudine (ZDV) ARV prophylaxis regimen can be used in newborns whose mothers received ART during pregnancy and had sustained viral suppression near delivery (defined as a confirmed HIV RNA level <50 copies/mL) and for whom there are no concerns related to maternal adherence (BII).
- Newborns at higher risk of perinatal acquisition of HIV should initiate presumptive HIV therapy (see Table 7 for recommended regimens). Newborns at higher risk of HIV acquisition include those born to women with HIV who:
 - Have not received antepartum or intrapartum ARV drugs (AI), or
 - Have received only intrapartum ARV drugs (AI), or
 - Have received antepartum ARV drugs but who did not achieve viral suppression near delivery (AII), or
 - Have primary or acute HIV infection during pregnancy (AII), or
 - Have primary or acute HIV infection while breastfeeding (AII).
- Newborns of women with unknown HIV statuses who test HIV positive on expedited testing during labor or shortly after birth should initiate an ARV regimen (either presumptive HIV therapy or two-drug ARV prophylaxis, based on clinician assessment of risk) (AII). If supplemental testing is negative, the ARV regimen should be discontinued (AII).
- For newborns with HIV infection, ART should be initiated (AI).
- The use of ARV drugs other than ZDV, lamivudine, and nevirapine cannot be recommended for any indication in premature newborns (<37 weeks gestational age) because of lack of dosing and safety data (BII).
- Providers with questions about ARV management of perinatal HIV exposure should consult the National Perinatal HIV Hotline (1-888-448-8765), which provides free clinical consultation on all aspects of perinatal HIV, including newborn care (AIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

General Considerations for Antiretroviral Management of Newborns Exposed to HIV or Born with HIV

All newborns with perinatal exposure to HIV should receive antiretroviral (ARV) drugs during the neonatal period to reduce the risk of perinatal HIV transmission, with selection of the appropriate ARV regimen guided by the level of transmission risk. HIV transmission can occur *in utero*, intrapartum, or during breastfeeding.

Maternal viral load is the most important risk factor for HIV transmission to a newborn. Newborns are at an increased risk of transmission when their mothers did not receive antiretroviral therapy (ART) during pregnancy, started antepartum treatment late in pregnancy, or when antepartum treatment did not result in virologic suppression. Higher maternal viral load, especially in late pregnancy, correlates with higher risk of transmission. There is a spectrum of transmission risk that depends on these and other maternal and infant factors, including mode of delivery, gestational age at delivery, and maternal health status.

Historically, the use of ARV drugs in the newborn period was referred to as ARV prophylaxis, since it primarily focused on protection against newborn perinatal acquisition of HIV. More recently, clinicians have begun to identify newborns at highest risk for HIV acquisition and initiate three-drug ARV regimens as **presumptive** treatment of HIV. In this section, the following terms will be used:

- **ARV Prophylaxis:** The administration of ARV drugs to a newborn without documented HIV infection to reduce the risk of HIV acquisition. ARV prophylaxis includes administration of a single agent, usually zidovudine (ZDV), as well as combinations of two or three ARV drugs.
- **Presumptive HIV Therapy:** The administration of a three-drug ARV regimen to newborns at highest risk of HIV acquisition. **Presumptive** HIV therapy is intended to be early treatment for a newborn who is later documented to have acquired HIV, but it also serves as ARV prophylaxis against HIV acquisition for those newborns who are exposed to HIV *in utero*, during the birthing process, or during breastfeeding and who do not acquire HIV.
- **HIV Therapy:** The administration of a three-drug ARV treatment regimen to newborns with documented HIV (see [Diagnosis of HIV Infection in Infants and Children](#)).

The terms ARV prophylaxis and **presumptive** HIV therapy describe the clinician's intent when prescribing ARV drugs, and there may be an overlap between these two terms. For example, a **presumptive** HIV therapy regimen also provides ARV prophylaxis for a newborn. However, two-drug (or sometimes three-drug) ARV prophylaxis regimens, notably those that use prophylactic doses rather than therapeutic doses of nevirapine (NVP), are not considered **presumptive** HIV therapy.

The interval during which newborn ARV prophylaxis or **presumptive** HIV therapy can be initiated and still be beneficial is undefined; however, most studies support providing ARV drugs as early as possible after delivery.¹⁻⁶

Table 6 provides an overview of neonatal ARV management recommendations according to risk of perinatal HIV transmission to the newborn, and Table 7 summarizes the recommendations for ARV drug dosing in newborns. Additional information about dose selection for newborns, including premature infants (<37 weeks gestational age), can be found in the [Pediatric Antiretroviral Guidelines](#). In addition, the [National Perinatal HIV Hotline](#) (1-888-448-8765) is a federally funded service that provides free clinical consultation on difficult cases to providers who are caring for pregnant women living with HIV and their newborns, and consultants can provide referrals to local or regional pediatric HIV specialists.

Table 6. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn

Drug selection and dosing considerations are related to the age and gestational age of the newborn. Consultation is available through the [National Perinatal HIV Hotline](https://aidsinfo.nih.gov/hotline) (1-888-448-8765).

Level of Perinatal HIV Transmission Risk	Description	Neonatal ARV Management
Low Risk of Perinatal HIV Transmission	Mothers who received ART during pregnancy with sustained viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) near delivery and no concerns related to adherence	ZDV for 4 weeks
Higher Risk of Perinatal HIV Transmission^{a,b}	Mothers who received neither antepartum nor intrapartum ARV drugs Mothers who received only intrapartum ARV drugs Mothers who received antepartum and intrapartum ARV drugs but who have detectable viral loads near delivery, particularly when delivery was vaginal Mothers with acute or primary HIV infection during pregnancy or breastfeeding (in which case, the mother should discontinue breastfeeding) ^c	Presumptive HIV therapy using either ZDV, 3TC, and NVP (treatment dose) <i>or</i> ZDV, 3TC, and RAL administered from birth up to 6 weeks. ^d
Presumed Newborn HIV Exposure	Mothers with unconfirmed HIV status who have at least one positive HIV test at delivery or postpartum <i>or</i> Whose newborns have a positive HIV antibody test	ARV management as described above for newborns with a higher risk of perinatal HIV transmission Infant ARV drugs should be discontinued immediately if supplemental testing confirms that the mother does not have HIV
Newborn with HIV^e	Positive newborn HIV virologic test/NAT	Three-drug ARV regimen using treatment doses

^a See text for evidence that supports the use of **presumptive** HIV therapy and a two-drug ARV prophylaxis regimen.

^b See [Intrapartum Care](#) for guidance on indications for scheduled cesarean delivery and intrapartum IV ZDV to reduce the risk of perinatal HIV transmission for mothers with an elevated viral load at delivery.

^c Most Panel members would opt to administer presumptive HIV therapy to infants whose mothers had acute HIV during pregnancy because of the higher risk for *in utero* transmission. If acute HIV is diagnosed during breastfeeding, the mother should stop breastfeeding.

^d The optimal duration of **presumptive** HIV therapy in newborns **who are at a** higher risk of perinatal HIV transmission is unknown. **If possible, newborns who are at a higher risk of HIV acquisition should receive ZDV for 6 weeks. Additional medications, such as 3TC, RAL, or NVP, may need to administered for 2 to 6 weeks; the recommended durations for these drugs vary based on HIV NAT results, maternal viral load at the time of delivery, and additional risk factors for HIV transmission. Consultation with an expert in pediatric HIV is recommended when selecting a therapy duration, as this decision should be based on case-specific risk factors and interim HIV NAT results. The two-drug regimen used in NICHD-HPTN 040/PACTG 1043 for infants who were at a higher risk of HIV acquisition is described in the text (see the Two-Drug Antiretroviral Prophylaxis section).**

^e Most Panel members do not recommend delaying the initiation of ART pending results of the confirmatory HIV NAT, given the low likelihood of a false-positive HIV NAT.

Note: ARV drugs should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery. See Table 7 for dosing specifics.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; IV = intravenous; NAT = nucleic acid test; NVP = nevirapine; the Panel = Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission; RAL = raltegravir; ZDV = zidovudine

Table 7. Antiretroviral Dosing Recommendations for Newborns (page 1 of 2)

Newborns at Low Risk of Perinatal HIV Transmission	
Recommended Regimen	Recommended Duration
ZDV	ZDV administered for 4 weeks at the doses listed below
Newborns at Higher Risk of Perinatal HIV Transmission	
Recommended Regimen	Recommended Duration
Three-drug HIV therapy: ZDV plus 3TC plus (NVP or RAL)	ZDV administered for 6 weeks, with no increase to the 12 mg/kg dose unless the infant has confirmed HIV infection. Dosing for 3TC, NVP, and RAL is described below. Duration for these three drugs may vary; see the guidance in footnote.^a
Newborns with HIV Infection	
Recommended Regimen	Lifelong Duration Recommended ^b
Three-drug HIV therapy: ZDV plus 3TC plus (NVP or RAL)	Lifelong therapy in accordance with current treatment guidelines. The ARV regimen should be individualized based on the infant's age and clinical determinants. NVP can be replaced with LPV/r when the infant reaches a postmenstrual age of ≥42 weeks (defined as the time from the first day of the mother's last menstrual period to birth plus the time elapsed after birth) and a postnatal age ≥14 days. NVP can be replaced with RAL at any age in infants who were born at a postmenstrual age of ≥37 weeks and who weigh ≥2 kg.

Drug	Drug Doses by Gestational Age at Birth								
ZDV	≥35 Weeks Gestation at Birth								
	<i>Birth to Age 4 Weeks:</i>								
	• ZDV 4 mg/kg per dose orally twice daily								
	<i>Age >4 Weeks:</i>								
	• ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.								
	Simplified Weight-Band Dosing for Newborns Aged ≥35 Weeks Gestation from Birth to 4 Weeks								
	<table><tr><th>Weight Band</th><th>Volume of ZDV 10 mg/mL Oral Syrup Twice Daily</th></tr><tr><td>2 to <3 kg</td><td>1 mL</td></tr><tr><td>3 to <4 kg</td><td>1.5 mL</td></tr><tr><td>4 to <5 kg</td><td>2 mL</td></tr></table>	Weight Band	Volume of ZDV 10 mg/mL Oral Syrup Twice Daily	2 to <3 kg	1 mL	3 to <4 kg	1.5 mL	4 to <5 kg	2 mL
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	<i>Birth to Age 2 Weeks:</i>								
	• ZDV 2 mg/kg per dose orally twice daily								
	<i>Age 2 Weeks to 6 to 8 Weeks:</i>								
	• ZDV 3 mg/kg per dose orally twice daily								
	<i>Age >6 to 8 Weeks:</i>								
	• ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.								
	<30 Weeks Gestation at Birth								
	<i>Birth to Age 4 Weeks:</i>								
	• ZDV 2 mg/kg per dose orally twice daily								
	<i>Age 4 to 8–10 Weeks:</i>								
	• ZDV 3 mg/kg per dose orally twice daily								
	<i>Age >8 to 10 Weeks:</i>								
	• ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection								
3TC	≥32 Weeks Gestation at Birth								
	<i>Birth to Age 4 Weeks:</i>								
	• 3TC 2 mg/kg per dose orally twice daily								
	<i>Age >4 Weeks:</i>								
	• 3TC 4 mg/kg per dose orally twice daily								

Table 7. Antiretroviral Dosing Recommendations for Newborns (page 2 of 2)

Drug	Drug Doses by Gestational Age at Birth																																
NVP	<p>≥37 Weeks Gestation at Birth</p> <p><i>Birth to Age 4 Weeks:</i></p> <ul style="list-style-type: none"> • NVP 6 mg/kg per dose orally twice daily^c <p><i>Age >4 Weeks:</i></p> <ul style="list-style-type: none"> • NVP 200 mg/m² of BSA per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection. 																																
	<p>≥34 to <37 Weeks Gestation at Birth</p> <p><i>Birth to Age 1 Week:</i></p> <ul style="list-style-type: none"> • NVP 4 mg/kg per dose orally twice daily <p><i>Age 1 to 4 Weeks:</i></p> <ul style="list-style-type: none"> • NVP 6 mg/kg per dose orally twice daily <p><i>Age >4 Weeks:</i></p> <ul style="list-style-type: none"> • NVP 200 mg/m² of BSA per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection. 																																
<p>RAL</p> <p>Note: If the mother has taken RAL 2–24 hours prior to delivery, the neonate's first dose of RAL should be delayed until 24–48 hours after birth; additional ARV drugs should be started as soon as possible.⁷</p>	<p>≥37 Weeks Gestation at Birth and Weighing ≥2 kgd</p> <p><i>Birth to Age 6 Weeks:</i></p> <table border="1"> <thead> <tr> <th>Body Weight</th><th>Volume (Dose) of RAL 10 mg/mL Suspension</th></tr> </thead> <tbody> <tr> <td colspan="2">Birth to 1 Week: Once-Daily Dosing</td></tr> <tr> <td colspan="2">Approximately 1.5 mg/kg per dose</td></tr> <tr> <td>2 to <3 kg</td><td>0.4 mL (4 mg) once daily</td></tr> <tr> <td>3 to <4 kg</td><td>0.5 mL (5 mg) once daily</td></tr> <tr> <td>4 to <5 kg</td><td>0.7 mL (7 mg) once daily</td></tr> <tr> <td colspan="2">1 to 4 Weeks: Twice-Daily Dosing</td></tr> <tr> <td colspan="2">Approximately 3 mg/kg per dose</td></tr> <tr> <td>2 to <3 kg</td><td>0.8 mL (8 mg) twice daily</td></tr> <tr> <td>3 to <4 kg</td><td>1 mL (10 mg) twice daily</td></tr> <tr> <td>4 to <5 kg</td><td>1.5 mL (15 mg) twice daily</td></tr> <tr> <td colspan="2">4 to 6 Weeks: Twice-Daily Dosing</td></tr> <tr> <td colspan="2">Approximately 6 mg/kg per dose</td></tr> <tr> <td>3 to <4 kg</td><td>2.5 mL (25 mg) twice daily</td></tr> <tr> <td>4 to <6 kg</td><td>3 mL (30 mg) twice daily</td></tr> <tr> <td>6 to <8 kg</td><td>4 mL (40 mg) twice daily</td></tr> </tbody> </table>	Body Weight	Volume (Dose) of RAL 10 mg/mL Suspension	Birth to 1 Week: Once-Daily Dosing		Approximately 1.5 mg/kg per dose		2 to <3 kg	0.4 mL (4 mg) once daily	3 to <4 kg	0.5 mL (5 mg) once daily	4 to <5 kg	0.7 mL (7 mg) once daily	1 to 4 Weeks: Twice-Daily Dosing		Approximately 3 mg/kg per dose		2 to <3 kg	0.8 mL (8 mg) twice daily	3 to <4 kg	1 mL (10 mg) twice daily	4 to <5 kg	1.5 mL (15 mg) twice daily	4 to 6 Weeks: Twice-Daily Dosing		Approximately 6 mg/kg per dose		3 to <4 kg	2.5 mL (25 mg) twice daily	4 to <6 kg	3 mL (30 mg) twice daily	6 to <8 kg	4 mL (40 mg) twice daily
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^a The optimal duration of presumptive HIV therapy in newborns who are at a higher risk of perinatal HIV transmission is unknown. If possible, newborns who are at a higher risk of HIV acquisition should receive ZDV for 6 weeks. Additional medications, such as 3TC, RAL, or NVP, may need to administered for 2 to 6 weeks; the recommended durations for these drugs vary based on HIV NAT results, maternal viral load at the time of delivery, and additional risk factors for HIV transmission. Consultation with an expert in pediatric HIV is recommended when selecting a therapy duration, as this decision should be based on case-specific risk factors and interim HIV NAT results. The two-drug regimen used in NICHD-HPTN 040/PACTG 1043 for infants who were at a higher risk of HIV acquisition is described in the text (see the Two-Drug Antiretroviral Prophylaxis section).

^b For ARV management after the newborn period, see the [Pediatric Antiretroviral Guidelines](#).

^c This dose is an investigational NVP treatment dose recommended by the Panel; the FDA has not approved a dose of NVP for infants aged <1 month. See the Two-Drug Antiretroviral Prophylaxis section for prophylactic NVP dosing if using the NICHD-HPTN 040/PACTG 1043 prophylaxis regimen.

^d RAL dosing is increased at 1 and 4 weeks of age because metabolism by UGT1A1 is low at birth and increases rapidly during the next 4–6 weeks of life. No dosing information is available for preterm infants or infants weighing <2 kg at birth.

Key: 3TC = lamivudine; ARV = antiretroviral; BSA = body surface area; FDA = Food and Drug Administration; IV = intravenous; LPV/r = lopinavir/ritonavir; NAT = nucleic acid test; NVP = nevirapine; the Panel = the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission; RAL = raltegravir; UGT = uridine diphosphate glucotransferase; ZDV = zidovudine

Recommendations for Antiretroviral Drugs in Specific Clinical Situations

In this section and Table 6, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) presents available data and recommendations for management of newborns with documented HIV and newborns born to mothers who:

- Received antepartum/intrapartum ARV drugs and achieved effective viral suppression
- Are at higher risk of transmitting HIV to their newborns, including mothers who:
 - Received neither antepartum nor intrapartum ARV drugs, *or*
 - Received only intrapartum ARV drugs, *or*
 - Received antepartum and intrapartum ARV drugs but who had detectable viral load near delivery, particularly if delivery was vaginal
- Had acute or primary HIV infection during pregnancy or breastfeeding
- Have unknown HIV status
- Have known ARV drug-resistant virus

Newborns Born to Mothers Who Achieved Viral Suppression on Antepartum/Intrapartum Antiretroviral Drugs

The risk of HIV acquisition in newborns born to women who received ART during pregnancy and labor and who had undetectable viral loads at delivery is <1%. In the PACTG 076 study, ZDV alone reduced the incidence of perinatal HIV transmission, and ZDV is recommended as prophylaxis for neonates whose mothers received ART that resulted in consistent virologic suppression during pregnancy. The optimal minimum duration of neonatal ZDV prophylaxis has not been established in clinical trials. A 6-week ZDV regimen was studied in newborns in PACTG 076. However, evidence that supports a reduced duration of ZDV prophylaxis in infants born to women who were virologically suppressed during pregnancy and at delivery is mounting.⁸⁻¹⁰ In the United Kingdom and many other European countries, a 2-week neonatal ZDV prophylaxis regimen is recommended for infants born to women who have been on ART for longer than 10 weeks **and** have had at least two documented maternal HIV viral loads <50 copies/mL at least 4 weeks apart **and** have viral loads <50 copies/mL at or after 36 weeks gestation. If all of these criteria are not fulfilled but the maternal viral load is <50 copies/mL at or after 36 weeks gestation, a 4-week course of ZDV is recommended.¹¹ Compared with the 6-week ZDV regimen, 2 to 4 weeks on a ZDV regimen has been reported to allow earlier recovery from anemia in otherwise healthy newborns.^{12,13}

Currently, the Panel recommends a 4-week neonatal ZDV prophylaxis regimen for newborns if the mother achieved viral suppression on ART during pregnancy (defined as a confirmed HIV RNA level <50 copies/mL) at or after 36 weeks gestation, and there are no concerns related to maternal adherence. Dosing recommendations for ZDV are available for premature newborns, and an intravenous preparation of ZDV is available. Table 7 shows recommended neonatal ZDV dosing based on gestational age and birth weight.

Newborns Born to Mothers Who Received No Antepartum or Intrapartum Antiretroviral Drugs, Who Received Intrapartum Antiretroviral Drugs Only, Who Received Antiretroviral Drugs and Were Not Virally Suppressed Near Delivery, or Who Acquired HIV During Pregnancy or Breastfeeding

The Panel recommends that all newborns born to mothers who had detectable viral loads at delivery, who received only intrapartum ARV drugs, or who received no ARV drugs during pregnancy or delivery are at higher risk of HIV acquisition and **should receive presumptive HIV therapy**.^{5,14-18} Primary or acute HIV infection during pregnancy is also associated with an increased risk of perinatal transmission of HIV. Infants born to women who acquired HIV during pregnancy **should receive presumptive HIV therapy** (see [Acute HIV Infection](#)). The experience with these two strategies is described below.

Presumptive HIV Therapy

Early effective treatment of HIV infection in infants restricts the viral reservoir size, reduces HIV genetic variability, and modifies the immune response.¹⁹⁻²⁴ As demonstrated with the “Mississippi baby” and other infants who were treated shortly after birth, early treatment may provide an opportunity for an “ART-free remission” of HIV infection.²⁵⁻²⁷ Because of these potential benefits of early ART, the Panel recommends a three-drug ARV **presumptive** HIV therapy regimen consisting of ZDV, lamivudine (3TC), and either NVP (at treatment dose) or raltegravir (RAL) for newborns at higher risk of perinatal acquisition of HIV.

Although no clinical trials have compared the safety and efficacy of **presumptive** ART with single-drug or two-drug regimens, emerging data suggests that early **presumptive** HIV therapy is not associated with serious adverse events. Many infants develop anemia or neutropenia that may be drug-related regardless of whether the ARV drugs are administered as prophylaxis or treatment.²⁸⁻³² In a prospective cohort in Thailand, infants who received an **presumptive** HIV therapy regimen that contained ZDV, 3TC, and NVP were more likely to have Grade 2 or higher anemia at 1 and 2 months of life compared to infants who received ZDV alone (48.5% vs. 32.3%; $P = 0.02$). However, there was no difference in the incidence of severe anemia between the two groups.³³ Additionally, in a Canadian study, nonspecific signs and symptoms (e.g., vomiting, diarrhea, rash, jitteriness, irritability) that were potentially attributable to medication-related adverse effects were reported among the newborns who received **presumptive** HIV therapy but not among those who received ZDV only (10.2% vs. 0%; $P < 0.001$). Infants were more likely to discontinue **presumptive** HIV therapy prematurely than a regimen of ZDV alone (9.5% vs. 2.1%; $P = 0.01$).²⁹

The Centers for Disease Control and Prevention recommend a three-drug ARV regimen for HIV-post-exposure prophylaxis following occupational and non-occupational HIV exposure. HIV acquisition risk in these circumstances is often lower than for newborns at higher risk of HIV acquisition.^{34,35} **Presumptive** HIV therapy pharmacokinetic (PK) and safety data has provided reassuring evidence for its use in the neonatal period. Although the use of NVP to prevent perinatal HIV transmission has been found to be safe in neonates and low-birthweight newborns, these prophylaxis-dose regimens target trough drug levels which are ≥ 10 -fold lower than targeted therapeutic levels. However, recent studies of therapeutic doses of NVP and RAL have established safe doses that achieve targeted PK parameters.³⁶⁻⁴⁰

At this time, if a **presumptive** HIV therapy regimen is required, the Panel recommends using a combination of ZDV, 3TC, and NVP (treatment dose) or ZDV, 3TC, and RAL (see **Tables 6 and 7**). The optimal duration of **presumptive** HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Some Panel members opt to discontinue additional medications if birth nucleic acid test (NAT) results are negative, while others would continue **presumptive** HIV therapy for 2 to 6 weeks depending on the risk of HIV transmission. In all cases, ZDV should be continued for 6 weeks. If HIV infection is confirmed and the infant is receiving NVP, a switch from NVP to lopinavir/ritonavir (LPV/r) is recommended when the infant reaches a postmenstrual age (defined as the time from the first day of the mother’s last menstrual period to birth plus the time elapsed after birth) of ≥ 42 weeks and a postnatal age of ≥ 14 days; a switch to RAL can be made at any age (see **What to Start** in the **Pediatric Antiretroviral Guidelines**). Consulting an expert in pediatric HIV is recommended when selecting a therapy duration based on case-specific risk factors and interim HIV NAT results.

Two-Drug Antiretroviral Prophylaxis

To date, the NICHD-HPTN 040/PACTG 1043 trial is the only randomized clinical trial of multi-ARV prophylaxis in newborns at higher risk of HIV acquisition. In this study, 1,746 formula-fed infants born to women with HIV who did not receive any ARV drugs during pregnancy were randomized to receive one of three newborn prophylaxis regimens: the standard 6-week ZDV regimen; 6 weeks of ZDV plus three doses of NVP given during the first week of life (first dose given at birth or within 48 hours of birth, second dose 48 hours after the first dose, and third dose 96 hours after the second dose); and 6 weeks of ZDV plus 2 weeks of 3TC plus nelfinavir (NFV).

Forty-one percent of the mothers received ZDV during labor. The risk of intrapartum transmission was significantly lower in the two-drug and three-drug arms (2.2% and 2.5%, respectively, vs. 4.9% for 6 weeks of ZDV alone; $P = 0.046$ for each experimental arm vs. ZDV alone).⁵ The NICHD-HPTN 040/PACTG 1043 regimen was associated with nucleoside reverse transcriptase inhibitor (NRTI) resistance in three of 53 participants (5.7%) with *in utero* infection who were treated with ZDV alone, and in six of 33 participants (18.2%) who were treated with ZDV plus NVP ($P > 0.05$). In addition, the third drug in the three-arm regimen was NFV, which has highly variable PKs in this age group and did not reach the NFV target plasma concentration in 46% of study participants.⁴¹

Although transmission rates with the two regimens were similar, neutropenia was significantly more common with the three-drug regimen than with the two-drug or ZDV-alone regimens (27.5% vs. 14.9% vs. 16.4%; $P < 0.001$ for both comparisons). For newborns who are at a higher risk of HIV acquisition, the **two-drug regimen used in NICHD-HPTN 040/PACTG 1043 is an option for preventing HIV transmission in infants aged ≥ 32 weeks gestation at birth who weigh ≥ 1.5 kg. This two-drug regimen consists of 6 weeks of ZDV plus three doses of the prophylactic dose of NVP, with the NVP doses given within 48 hours of birth, 48 hours after the first dose, and 96 hours after the second dose. The prophylactic doses are NVP 12 mg per dose orally for infants weighing > 2 kg and NVP 8 mg per dose orally for infants weighing 1.5 kg to 2 kg. These are the actual doses, not the mg/kg doses. ZDV dosing is shown in Table 7.**

Choosing between Presumptive HIV Therapy and **Two-Drug** Antiretroviral Prophylaxis

Because there is a spectrum of transmission risk that depends on maternal viral load and other maternal and infant factors **and** there are no randomized trials that have compared the safety and efficacy of **presumptive** HIV therapy and **two-drug** ARV prophylaxis, experts have differing opinions about when to initiate **presumptive** HIV therapy and when to initiate **two-drug** prophylaxis. For instance, among women who received ARV drugs during pregnancy but who have a detectable viral load near delivery (on or after 36 weeks gestation), the level of maternal viremia that would prompt the use of a **two-drug** ARV prophylaxis regimen or **presumptive** HIV therapy is not definitively known.

In two large observational studies of women on combination antenatal ARV drugs, perinatal transmission rates were 0.05% and 0.3% when the mother had a viral load < 50 copies/mL at delivery. Rates of transmission **in these studies** increased to 1.1% and 1.5% when viral load was 50 to 399 copies/mL, and 2.8% and 4.1% when viral load was > 400 copies/mL.^{42,43} While **most Panel members** would recommend initiating **presumptive** HIV therapy with any detectable level of viremia near delivery, others may opt for a **two-drug** prophylaxis regimen if maternal viral load was less than 200 to 400 copies/mL. **Emerging data about the lack of serious safety issues associated with presumptive** HIV therapy in newborns is reassuring, even though nonserious adverse events may occur more frequently.

In summary, in scenarios where the infant is at higher risk of HIV transmission, **most Panel members recommend presumptive HIV therapy. In some situations, a two-drug ARV prophylaxis regimen may be considered, see Two-Drug Antiretroviral Prophylaxis in the text.** Choosing between these regimens will depend on the clinician's assessment of the likelihood of HIV transmission, and a decision should be made after weighing the risks and benefits of the proposed regimen and discussing these transmission prevention strategies with the parents.

Consulting an expert in pediatric HIV or the [National Perinatal HIV Hotline](https://www.hivhotline.org/) (1-888-448-8765) is recommended when selecting a regimen based on case-specific risk factors.

Newborns Born to Mothers with Unknown HIV Status Who Present in Labor

Expedited HIV testing is recommended during labor for women with unknown HIV status; if testing is not performed during labor, it should be performed as soon as possible after birth for the mothers and/or their newborns (see [Maternal HIV Testing and Identification of Perinatal HIV Exposure](#)). Expedited test results should be available within 60 minutes. If maternal or infant expedited testing is positive, the newborn **should**

immediately initiate presumptive HIV therapy, without waiting for the results of supplemental tests. Expedited HIV testing should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care unit or special care or newborn nursery.

A positive initial test result in mothers or newborns should be presumed to indicate maternal HIV until supplemental testing clarifies maternal and newborn status. If appropriate test results for a mother (or newborn) are negative, newborn ARV drugs can be discontinued. Clinicians should be aware of their state laws, as not all states allow HIV testing in infants without parental consent.

A nursing mother who is suspected of having HIV based on an initial positive antibody or antibody/antigen test result should stop breastfeeding until HIV is confirmed or ruled out.

Pumping and temporarily discarding or freezing breast milk can be recommended. If HIV is ruled out, breastfeeding can resume. If HIV is confirmed, breastfeeding should be discontinued permanently.⁴⁴

Newborns Born to Mothers with Antiretroviral Drug-Resistant Virus

The optimal ARV regimen for newborns born to women with ARV drug-resistant virus is unknown. Although some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility,⁴⁵ perinatal transmission of multidrug-resistant virus does occur.⁴⁶⁻⁵¹ It is also unknown whether resistant virus in the mother increases the antepartum/intrapartum risk of HIV acquisition by the infant. A recently reported secondary analysis of data from the NICHD-HPTN 040/PACTG 1043 study demonstrated that the risk of perinatal transmission was not related to the presence of drug resistance mutations in mothers who had not received ARV drugs prior to the start of the study (adjusted odds ratio 0.8; 95% confidence interval, 0.4–1.5).⁵¹ The ARV regimen for newborns born to mothers with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist before delivery, or through consultation via the [National Perinatal HIV Hotline](https://www.hivhotline.org/) (1-888-448-8765). However, there is no evidence that neonatal prophylaxis regimens customized based on presence of maternal drug resistance are more effective than standard neonatal prophylaxis regimens.

Newborns with HIV Infection

Until recently, neonatal ARV regimens were designed for prophylaxis against perinatal HIV transmission and were intended to be as simple as possible for practical use. There was little reason to develop ARV regimens for treatment of neonates, as the long turnaround times to receive HIV NAT results meant that neonatal infections were generally not diagnosed during the first weeks of life. HIV NAT results are now available within a few days, and HIV in newborns is being diagnosed as early as the first days of life in many centers. A positive HIV NAT must be repeated to confirm HIV. However, most Panel members do not recommend delaying the initiation of ART while waiting for the results of the confirmatory HIV NAT, given the low likelihood of a false-positive HIV NAT. However, evidence that early treatment (before age 2 weeks) will conclusively lead to prolonged remission or better outcomes in newborns with HIV is lacking.

Information regarding the safety of early treatment of HIV in newborns has been reported from two studies. In the IMPAACT P1115 study, 54 infants with HIV initiated **presumptive** HIV therapy between 0.4 and 40 hours of life. Grade 3 or 4 related events, most of which were hematologic, occurred in 22 of 54 infants (41%) through 52 weeks of the study.³⁰ Forty infants with HIV in Botswana initiated NVP plus ZDV plus 3TC at a median age of 2 days (range 1–5 days) and transitioned to LPV/r plus ZDV plus 3TC at approximately 2 weeks of age. These infants had minimal toxicity during the first 12 weeks of treatment. Only one instance of Grade 3 neutropenia was reported and no instances of Grade 3 or 4 anemia were reported.³²

Earlier diagnosis of HIV in newborns and the increasing use of **presumptive** HIV therapy in newborns at higher risk for HIV acquisition have necessitated investigation of dosing and safety of ARV drugs in term and preterm newborns. Although data are still incomplete, especially for preterm newborns, PK and safety profiles of ARV drugs are increasingly available. As already noted, the recommended neonatal ARV doses for prophylaxis and for treatment are the same, with the important exception of [NVP](#) (see the [Pediatric Antiretroviral Guidelines](#)).

Sufficient data exist to provide dosing recommendations for the treatment of HIV in neonates using the following medications (see the [Pediatric Antiretroviral Guidelines](#)):

- From birth in term and preterm newborns: [ZDV](#), [3TC](#), [NVP](#)
- From birth in term newborns: [emtricitabine](#), [RAL](#)
- From age 2 weeks in term newborns: [LPV/r](#)

Dosing recommendations for *premature* newborns are available for ZDV, 3TC, and NVP only. Neonatal dosing advice, including dosing advice for premature newborns, is summarized in Table 7. For more detailed information about neonatal dosing recommendations and considerations when using these drugs, please see the [Pediatric Antiretroviral Guidelines](#).

Newborns of Mothers Who Receive an HIV Diagnosis while Breastfeeding

Women with suspected HIV (e.g., a positive initial screening test) should stop breastfeeding until HIV is ruled out. Pumping and temporarily discarding or freezing breast milk can be recommended to mothers who are suspected of having HIV but whose HIV serostatus is not yet confirmed and who want to continue to breastfeed. If HIV is ruled out, breastfeeding can resume. Breastfeeding **is not recommended** for women with confirmed HIV in the United States, including those receiving ART (see [Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed](#)).⁵²

The risk of HIV acquisition associated with breastfeeding depends on multiple newborn and maternal factors, including maternal viral load and CD4 T lymphocyte (CD4) cell count.⁵³ Newborns of women who develop acute HIV while breastfeeding are at greater risk of acquiring HIV than those whose mothers have chronic HIV infection,⁵⁴ because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 count.⁵⁵

Other than discontinuing breastfeeding, optimal strategies for managing a newborn who was breastfed by a mother with HIV (often because the mother just learned of her own HIV diagnosis) have yet to be defined. Some Panel members would consider the use of post-exposure prophylaxis in newborns for 4 to 6 weeks after cessation of breastfeeding. Post-exposure prophylaxis, however, is less likely to be effective in this circumstance than with other non-occupational exposures, because the exposure to breast milk is likely to have occurred over a prolonged period rather than during a single exposure to the virus.⁵⁶

Several studies of newborns who were breastfed by women with chronic HIV infection in low-resource settings have shown that daily newborn NVP, 3TC, LPV/r, or NVP plus ZDV can reduce the risk of postnatal infection during breastfeeding.⁵⁷⁻⁶¹ No trials have evaluated the use of multidrug-regimens to prevent transmission after cessation of breastfeeding in mothers with acute HIV infection.

Given the higher risk of postnatal transmission from a breastfeeding woman with acute HIV infection, an alternative approach favored by some Panel members is to offer **presumptive** HIV therapy until the infant's HIV status can be determined. If the infant's initial HIV NAT is negative, the optimal duration of **presumptive** HIV therapy is unknown. A 28-day course may be reasonable based on current recommendations for non-occupational HIV exposure.⁵⁶ When making decisions about ARV management, clinicians should consult a pediatric HIV specialist and counsel the parents on the potential risks and benefits of a particular treatment strategy. The [National Perinatal HIV Hotline](#) (1-888-448-8765) can provide referrals to local or regional pediatric HIV specialists.

Newborns exposed to HIV during breastfeeding should be tested for HIV infection prior to initiating **presumptive** HIV therapy, as well as 4 to 6 weeks and 4 to 6 months after diagnosis of maternal HIV infection and cessation of breastfeeding. An additional virologic test should be performed 2 to 4 weeks after discontinuing **presumptive** HIV therapy (see [Diagnosis of HIV Infection in Infants and Children](#)). If an HIV-exposed newborn is already receiving an ARV prophylaxis regimen other than **presumptive** HIV therapy and is found to have HIV, prophylaxis should be discontinued and treatment for HIV should be initiated.

Resistance testing should be performed, and the ART regimen should be modified if needed (see the [Pediatric Antiretroviral Guidelines](#)).

Short-Term Antiretroviral Drug Safety

Newborn prophylaxis with ZDV has been associated with only minimal toxicity, primarily transient hematologic toxicity (mainly anemia), which generally resolves by age 12 weeks (see [Initial Postnatal Management of the Neonate Exposed to HIV](#)). Data on toxicities in newborns who were exposed to multiple ARV drugs are limited.

Other than ZDV, 3TC is the NRTI with the most clinical experience for neonatal prophylaxis. In early studies, neonatal exposure to combination ZDV/3TC was generally limited to 1^{17,62,63} or 2 weeks.⁵ Six weeks of ZDV/3TC exposure in newborns has also been reported. These studies suggest that hematologic toxicity may be greater with ZDV/3TC than with ZDV alone, although the newborns in these studies also had *in utero* exposure to maternal HIV therapy that may have contributed to the toxicity.

In a French study, more cases of severe anemia and neutropenia were observed in newborns who were exposed to 6 weeks of ZDV/3TC for prophylaxis plus maternal antepartum ZDV/3TC than in a historical cohort of newborns who were exposed only to maternal and newborn ZDV. Anemia was reported in 15% of newborns and neutropenia was reported in 18% of newborns who were exposed to ZDV/3TC, with 2% of newborns requiring blood transfusion and 4% requiring treatment discontinuation for toxicity.⁶⁴ Similarly, in a Brazilian study of maternal antepartum ZDV/3TC and 6-week newborn ZDV/3TC prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69% and neutropenia seen in 13% of newborns.⁶⁵

Experience with other NRTI drugs for neonatal prophylaxis is more limited.^{66,67} Hematologic and mitochondrial toxicity may be more common with exposure to multiple NRTI drugs than with exposure to a single NRTI.^{64,68-71}

In rare cases, chronic multiple-dose NVP prophylaxis in pregnant women has been associated with severe and potentially life-threatening rash and hepatic toxicity.⁷² These toxicities have not been observed in newborns receiving prophylactic dosing with single-dose NVP or the two-drug ZDV regimen plus three doses of NVP in the first week of life used in NICHD-HPTN 040/PACTG 1043, or in breastfeeding newborns receiving NVP prophylaxis daily for 6 weeks to 18 months to prevent transmission of HIV via breast milk.^{5,57-59,61,73}

The Food and Drug Administration (FDA) recently approved infant dosing of RAL for term neonates aged ≥ 37 weeks gestation at birth and weighing ≥ 2 kg. Dosing information for RAL is not available for preterm or low birthweight infants. Infant RAL dosing needs to be increased at 1 week and 4 weeks of age. RAL is metabolized by uridine diphosphate glucuronosyltransferase (UGT) 1A1, the same enzyme responsible for the elimination of bilirubin. UGT enzyme activity is low at birth, and RAL elimination is prolonged in neonates. In addition, bilirubin and RAL may compete for albumin binding sites, and extremely elevated neonatal plasma RAL concentrations could pose a risk of kernicterus.⁷⁴ IMPAACT P1110 is a Phase 1, multicenter trial that enrolled full-term neonates who were exposed to HIV and who were at risk of acquiring perinatal HIV-1 infection, with or without *in utero* RAL exposure. Daily RAL was safe and well tolerated during the first 6 weeks of life. Infants were treated for ≤ 6 weeks from birth and followed for 24 weeks. There were no drug-related clinical adverse reactions, and only three laboratory adverse reactions were observed: one case of Grade 4 transient neutropenia in an infant receiving a ZDV-containing regimen; and two cases of bilirubin elevations (one Grade 1 and one Grade 2) that were considered nonserious and did not require specific therapy⁷⁵ (see the [Raltegravir](#) section of the [Pediatric Antiretroviral Guidelines](#) for additional information).

The safety and PK data on daily dosing from P1110 are from RAL-naïve infants whose mothers did not receive RAL; data collection from infants born to mothers who were receiving RAL is ongoing. However, the FDA currently recommends delaying the first dose of RAL in infants for 24 to 48 hours after birth if the mother received RAL 2 to 24 hours before delivery, and the Panel believes that this recommendation is reasonable based on current data about clearance of the drug in RAL-exposed infants.

Of the protease inhibitors, pediatric drug formulations are available for LPV/r, ritonavir (RTV), darunavir, tipranavir, and fosamprenavir; however, the use of these drugs in neonates during the first weeks of life **is not recommended** given the lack of dosing and safety information. In addition, LPV/r oral solution contains 42.4% alcohol and 15.3% propylene glycol. The enzymes that metabolize these compounds are immature in neonates, particularly preterm newborns. Four premature newborns (two sets of twins) who initiated LPV/r at birth developed heart block that resolved after drug discontinuation.^{76,77} In studies of adults, both RTV and LPV/r caused dose-dependent prolongation of the PR interval, and cases of significant heart block, including complete heart block, have been reported.

Elevation of 17-hydroxyprogesterone and dehydroepiandrosterone-sulfate has also been associated with administering LPV/r during the neonatal period, an association not found with ZDV. Levels of 17-hydroxyprogesterone were greater in newborns who were also exposed to LPV/r *in utero* than in those exposed only during the neonatal period. Term newborns were asymptomatic, but three premature newborns experienced life-threatening symptoms compatible with adrenal insufficiency, including hyponatremia and hyperkalemia with, in one case, cardiogenic shock.⁷⁸

On the basis of these and other post-marketing reports of cardiac toxicity (including complete atrioventricular block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, adrenal dysfunction, central nervous system depression, respiratory complications leading to death, and metabolic toxicity,⁷⁹ predominantly in preterm neonates, the FDA now recommends that LPV/r oral solution **not be administered** to neonates before the infant reaches a postmenstrual age (defined as time from the first day of the mother's last menstrual period to birth plus the time elapsed after birth) of ≥ 42 weeks and a postnatal age of ≥ 14 days.⁸⁰ However, the ANRS 12174 study randomized 1,273 newborns to receive either LPV/r (n = 615) or 3TC (n = 621) as prophylaxis during breastfeeding in women with CD4 counts above the local threshold for treatment at the time. Newborn study prophylaxis was initiated at 7 days of life, and only newborns weighing > 2 kg were randomized. The frequency of clinical and biological severe adverse events did not differ between the groups, suggesting that LPV/r is safe to use in term newborns aged 7 days and older.⁸¹ At this time, the Panel **does not recommend** the use of LPV/r before a postmenstrual age of 42 weeks (defined as time from the first day of the mother's last menstrual period to birth plus the time elapsed after birth) and a postnatal age of ≥ 14 days.

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